EFFICIENT STEREOSELECTIVE SYNTHESIS OF (2S,3S,5R)-(+)-PREUSSIN

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Abstract - Allyltrimethylsilane reacted with N-carbobenzoxy-L-phenylalaninal to afford with high diastereoselectivity syn-adduct which was subsequently transformed into (2S,3S,5R)-(+)-preussin.

Stereocontrolled transformation of α–amino acids has long been of great interest due to their importance as chiral building blocks in the synthesis of biologically active molecules.1 In our recent studies involving the synthesis of antibiotic amino sugars, we have found that suitably protected α–amino aldehydes are very convenient and versatile chirons.2 For example, addition of allyltrimethylsilane to N-mono- and N,N-diprotected α–amino aldehydes offers an easy access to almost enantiomerically pure both syn- and anti-adducts3 which are readily transformed into natural products, such as 3-hydroxyproline,4 1,3-dideoxyojirimycin,5 and statine.6

Now we report a new application of our methodology to the stereoselective and short synthesis of (2S,3S,5R)-(+)-preussin (1),7 also known as L-657,398,8 a naturally occurring pyrrolidine alkaloid isolated from the fermentation of Aspergillus ochraceus ATCC 22947 and Preussia sp., a similar but better antifungal agent, as compared with anisomycin. Since pioneering synthesis by Pak et al.9 several asymmetric syntheses of 1 have been reported.10

Retrosynthetic analysis, shown in Scheme 1, suggested that N-carbobenzoxy-L-phenylalaninal (5)11 and allyltrimethylsilane could serve as starting materials.

Addition of allyltrimethylsilane to aldehyde (5) in the presence of one equiv. of SnCl4 at -78°C, afforded with very high diastereoselectivity (98:2) the syn-adduct (4)13 in 77% yield. Olefin (4) was subjected to the vanadium-catalyzed epoxidation reaction,14 furnishing in 87% yield a chromatographically unseparable mixture of diastereoisomeric epoxides (3a) (syn) and (3b) (anti) in a ratio of 7:3. Hydrogenation of this mixture on palladium on charcoal as a catalyst caused deprotection of the amino

* Dedicated to Professor Sho Ito on the occasion of his 77th birthday.
group and subsequent cyclization to afford a mixture of diastereoisomeric pyrrolidines, which was treated with methyl chloroformate and subjected to chromatographic separation to give two pure diastereoisomers (2a)\(^\text{15}\) and (2b) in the same ratio as in the case of their precursors (3a) and (3b) (Scheme 2). The major diastereoisomer (2a), isolated in 59% yield, calculated on a starting mixture of epoxides (3), was oxidized using the TEMPO procedure\(^\text{12}\) to furnish the known aldehyde (6).\(^\text{9}\) Final transformation of 6 via the Wittig reaction with n-C\(_8\)H\(_{17}\)P\(^+\)Ph\(_3\)I, followed by Pd/C hydrogenation and LiAlH\(_4\) reduction afforded the desired (2S,3S,5R)-(+)–preussin (1)\(^\text{16}\) in good overall yield and correct stereochemistry.

Scheme 2. Reagents and conditions: (a) AllSi(CH\(_3\))\(_3\), SnCl\(_4\), CH\(_2\)Cl\(_2\), -78\(^\circ\)C, 77%; (b) t-C\(_4\)H\(_9\)OOH, VO(acac)_2 cat., CH\(_2\)Cl\(_2\), rt, 87%; (c) H\(_2\), 5% Pd/C, CH\(_3\)OH, rt, quant.; (d) ClCO\(_2\)CH\(_3\), CH\(_2\)Cl\(_2\), sat. aq NaHCO\(_3\), rt, 83%; (e) sat. aq NaHCO\(_3\), 4% aq NaOCl, 10% aq NaBr, TEMPO cat., AcOC\(_2\)H\(_5\)-PhCH\(_3\) 1:1, -5\(^\circ\)C, 72%; (f) n-C\(_8\)H\(_{17}\)P\(^+\)Ph\(_3\)I, n-C\(_4\)H\(_9\)Li, THF/HMPA 9:1, -78\(^\circ\)C, 80%; (h) LiAlH\(_4\), THF, reflux, 85%. 

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Scheme 1 Retrosynthetic analysis
It is noteworthy that allyl addition to \(N\)-Bn-\(N\)-Cbz analogue of 5, carried out under Barbier conditions,\(^3\) afforded the appropriate anti-adduct with good selectivity (86:14) and in high yield (98%). The \(\text{syn}\)-adduct (4) and its anti-isomer as well as their \(N\)-Bn-\(N\)-Cbz analogues can undergo the catalytic \(\text{VO(acac)}_2/\text{t-C}_4\text{H}_9\text{OOH}\) epoxidation with \(\text{syn}\)-selectivity or the \(\text{AI(Ot-C}_4\text{H}_9)_3/\text{t-C}_4\text{H}_9\text{OOH}\) epoxidation with high \(\text{anti}\)-selectivity. Combination of those possibilities provides selective access to all diastereoisomers of 2 and, as a consequence, to all diastereoisomers of preussin.

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REFERENCES AND NOTES


11. The L-phenylalanine derivative (5) was obtained in 87% overall yield on the following route: L-phenylalanine methyl ester hydrochloride was treated with benzyl chloroformate in the presence of sodium bicarbonate, affording N-Cbz-L-phenylalanine methyl ester which was then reduced with LiBH₄ to give N-Cbz-L-phenylalaninol. Finally, oxidation of this amino alcohol using the TEMPO procedure afforded the desired aldehyde (5).


13. Selected data: mp 62-64°C (CH₂Cl₂/hexane); [α]₀D –35.0° (c 1.0, CHCl₃); LSIMS HR calcd for (M+H)+ (C₂₀H₂₄NO₃) 326.1756, found 326.1791; ¹H NMR (500 MHz, CDCl₃): 7.31-7.21 (m, 10H), 5.73 (m, 1H), 5.17 (d, J=9.2 Hz, 1H), 5.12-5.03 (m, 4H), 3.90-3.75 (m, 1H), 3.64-3.57 (m, 1H), 2.96-2.83 (m, 2H), 2.27-2.16 (m, 2H), 2.05 (d, J=3.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): 156.42, 138.10, 136.56, 134.17, 129.30, 128.48, 128.04, 127.94, 126.42, 118.68, 69.83, 65.73, 39.22, 38.84.


15. Selected data: mp 84-87°C (CH₂Cl₂/hexane); [α]₀D –35.2° (c 1.0, CHCl₃); EIMS HR calcd for M⁺ (C₁₄H₁₉NO₄) 265.1314, found 265.1282; ¹H NMR (500 MHz, DMSO-d₆): 7.27-7.11 (m, 5H), 5.20 (d, J=5.4 Hz, 1H), 4.94 (br s, 1H), 4.15-4.02 (m, 1H), 3.89 (q, J=6.6 Hz, 1H), 3.79-3.67 (m, 1H), 3.60-3.49 (m, 2H), 3.30 (s, 3H), 2.92 (dd, J=13.1, 6.7 Hz, 1H), 2.13-2.05 (m, 1H), 1.86-1.80 (m, 1H); ¹³C NMR (125 MHz, DMSO-d₆): 155.60, 140.06, 129.35, 127.69, 125.41, 69.16, 62.51, 57.83, 51.52, 34.63.

16. Selected data: [α]₀D +23.4° (c 2.0, CHCl₃) [lit., 7 [α]₀D +22.0° (c 1.0, CHCl₃)]; LSIMS HR calcd for (M+H)+ (C₂₁H₃₆NO) 318.2797, found 318.2792; ¹H NMR (500 MHz, CDCl₃): 7.31-7.17 (m, 5H), 3.85-3.77 (m, 1H), 2.89 (dd, J=13.2, 10.1 Hz, 1H), 2.84 (dd, J=13.2, 4.6 Hz, 1H), 2.33 (s, 3H), 2.31-2.25 (m, 1H), 2.24-2.09 (m, 2H), 2.07-1.92 (br s, 1H), 1.76-1.68 (m, 1H), 1.46-1.40 (m, 1H), 1.37-1.21 (m, 15H), 0.88 (t, J=6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): 139.42, 129.34, 128.36, 126.05, 73.61, 70.45, 65.83, 39.31, 38.57, 34.88, 33.67, 31.87, 29.88, 29.61, 29.55, 29.29, 26.27, 22.66, 14.08.